Amendments to the Specification

Please amend the paragraphs below as follows:

Page 46, Paragraph beginning on Line 6.

A preferred simulation engine permits concurrent model building and simulation. An example is the program STELLA® (High Performance Systems, Inc.). STELLA® (differential equation solving program) is an interpretive program that can use three different numerical schemes to evaluate the differential equations: Euler's method, Runge-Kutta 2, or Runge-Kutta 4. The Kinetica™ program (InnaPhase, Inc.) is another differential equation solving program that can evaluate the equations of the model. By translating the model from a STELLA® (differential equation solving program) readable format to a Kinetica™ (differential equation solving program) readable format, physiological simulations can be constructed using Kinetica™ (differential equation solving program), which has various fitting algorithms. This procedure can be utilized when the adjustment parameters are being optimized in a stepwise fashion.

Page 48, Paragraph beginning on Line 17.

The basic structure of a physiological model and mathematical representation of its interrelated anatomical segments can be constructed using any number of techniques. The preferred techniques employ graphical-oriented compartment-flow model development computer programs such as STELLA®, KINETICA™ (differential equation solving programs) and the like. Many such programs are available, and most employ graphical user interfaces for model building and manipulation. In essence, symbols used by the programs for elements of the model are arranged by the user to assemble a diagram of the system or process to be modeled. Each factor in the model may be programmed as a numerical constant, a linear or non-linear relationship between two parameters or as logic statement. The model development

program then generates the differential equations corresponding to the user constructed model. For example, STELLA® (differential equation solving program) employs five basic graphic tools that are linked to create the basic structure of a model: (1) stocks; (2) flows; (3) converters; (4) input links; and (5) infinite stocks (See, e.g., Peterson *et al.*, STELLA® II, Technical Documentation, High Performance Systems, Inc., (1993)). Stock are boxes that represent a reservoir or compartment. Flows or flow regulators control variables capable of altering the state of compartment variables, and can be both uni-and bi-directional in terms of flow regulation. Thus, the flow/flow regulators regulate movement into and out of compartments. Converters modify flow regulators or other converters. Converters function to hold or calculate parameter variable values that can be used as constants or variables which describe equations, inputs and/or outputs. Converters allow calculation of parameters using compartment values. Input links serve as the internal communication or connective "wiring" for the model. The input links direct action between compartments, flow regulators, and converters. In calculus parlance, flows represent time derivatives; stocks are the integrals (or accumulations) of flows over time; and converters contain the micro-logic of flows. The stocks are represented as finite difference equations having the following form: Stock(t) = Stock(t-dt) + (Flow)*dt. Rewriting this equation with timescripts and substituting t for dt: $Stock_t = Stock_{t-\Delta t} + \Delta t*(Flow)$. Re-arranging terms: $(Stock_t - Stock_{t-\Delta t})/\Delta t = Flow$, where "Flow" is the change in the variable "Stock" over the time interval "t." In the limit as Δt goes to zero, the difference equation becomes the differential equation: d(Stock)dt = Flow. Expressing this in integral notation: Stock = $\int$Flow dt. For higher-order equations, the higher-order differentials are expressed as a series of first-order equations. Thus, computer programs such as STELLA® (differential equation solving program) can be utilized to generate physiologic-based multi-compartment models as compartment-flow models using graphical tools and supplying the relevant differential equations of pharmacokinetics for the given physiologic system under investigation. An example of iconic tools and description, as well as graphically depicted compartment-flow models generated using STELLA® (differential

equation solving program) and their relation to a conventional pharmacokinetic IV model is illustrated in **Figure 6-9.**

Page 49, Paragraph beginning on Line 22.

The model components may include variable descriptors. Variable descriptors for STELLA® (differential equation solving program), for example, include a broad assortment of mathematical, statistical, and built in logic functions such as boolean and time functions, as well as user-defined constants or graphical relationships. This includes control statements, e.g., AND, OR, IF, ... THEN... ELSE, delay and pulsing, that allow for development of a set of production rules that the program uses to control the model. Variable descriptors are inserted into the "converters" and connected using "input links." This makes it is possible to develop complex rule sets to control flow through the model. The amount of time required to complete one model cycle is accomplished by inputting a total run time and a time increment (dt). The STELLA® (differential equation solving program) program then calculates the value of every parameter in the model at each successive time increment using Runge-Kutta or Euler's simulation techniques. The preferred simulation technique is Runge-Kutta. Once a model is built, it can be modified and further refined, or adapted or reconstructed by other methods, including manually, by compiling, or translated to other computer languages and the like depending on its intended end use.

Page 54, Paragraph beginning on Line 17.

An integrated physiological model corresponding to the GI tract of a mammal constructed using STELLA® (differential equation solving program) and the above-described methodology is illustrated in **Figures 25-26 and 30-40.** An example of information provided by the database is illustrated in **Appendix 4** for the gastrointestinal model depicted in **Figures 25-26** and **30-40**.

Page 60, Paragraph beginning on Line 19.

A computer-based mathematical model development tool with a graphical user interface was employed to design and construct the initial simulation models. The computer program STELLA® (differential equation solving program) was selected as suitable for this purpose since it permitted compartment model building and mathematical equation modification and at each stage of the build, as well as calculation of flow between compartments at user-specified time intervals (dt) with user-specified input functions and values. An example of iconic tools and description, as well as graphically depicted compartment-flow models generated using STELLA® (differential equation solving program) and their relation to a conventional pharmacokinetic IV model is illustrated in **Figures 6-9.**

Page 93, Paragraph beginning on Line 19.

The initial adjustment parameter values were determined empirically. Using a limited set of compounds and corresponding *in vitro* data from rabbit tissue, the adjustment parameters were manually varied to obtain FDp values that were reasonably consistent with the actual PK data. After the initial values were determined, the GI model developed using STELLA® (differential equation solving program) was converted to a program file readable by a program having fitting algorithm, such as KINETICA™ (differential equation solving program). The initial adjustment parameters were then simultaneously fit using non-linear regression analysis in a stepwise manner to determine optimized values (i.e., best fit values) for the adjustment parameters. Within each step, a few parameters were selected for optimization by simultaneous fitting. The fitting was approached using an iterative process, where selected adjustment parameters were varied systematically such that the deviation of the GI model determined absorption from the actual PK determined absorption was minimized. Once the deviation was reduced to a satisfactory level, few more parameters were then selected and

optimized. The process was continued until all parameters were successfully optimized. The new parameters were then placed into the GI model and the FDp determined for each compound which is compared to the PK FDp to establish the goodness of fit. This process was repeated until an acceptable goodness of fit was established. Using this approach, adjustment parameters were developed to correlate, for example, *in vitro* solubility, dissolution, dose and permeability in rabbits to *in vivo* human absorption. Although FDp was employed as the reference for deviation, the actual measurement of absorption can be evaluated using any number of parameters, such as plasma levels, absorption constants, or others. Moreover, it will be appreciated that many sets of adjustment parameters may be developed and established. For instance, others sets of adjustment parameters may be established to correlate dog, rat, monkey, or other species permeability data to human, dog, rat, rabbit, monkey, or other animal *in vivo* absorption.